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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/804,584	03/12/2001	Matthew L. Albert	600-1-276 CIP	5033

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EXAMINER
CANELLA, KAREN A

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 08/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/804,584	ALBERT ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-41* is/are pending in the application.

4a) Of the above claim(s) *5-14,20 and 23-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,15-19,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.08

DETAILED ACTION

Claim 4 has been amended. Claims 1, 2 and 4-41 are pending. Claims 23-41, drawn to non-elected inventions, remain withdrawn from consideration. Claims 5-14 and 20, drawn to non-elected species, remain withdrawn until such time as claims drawn to the elected species are deemed allowable. Claims 1, 2, 4, 15-19, 21 and 22 are under consideration.

Text of Title 35, U.S. Code not found in this action, can be found in a previous action.

Applicant has argued that the previous rejections over Albert et al (US 2002/014396) were improper as Albert et al have benefit of the same priority document, 09/251,896). This has been considered and found persuasive. However, as stated in the office action mailed March 1, 2004:

Acknowledgement is made of applicants claim to the priority documents of 60/075,356, filed February 20, 1998, 60/077,095, filed March 6, 1998 and 60/101,749, filed September 24, 1998. After review and reconsideration of these provisional application it is concluded that they do not provide adequate written description for the instant invention. 60/075,356 and 60/077,095, although providing a written description of cross presentation of antigens via dendritic cells which are exposed to apoptotic cells having said antigen, makes o reference to a method of inducing tolerance to said antigen by exposing the dendritic cells to apoptotic cells without helper T-cells. 60/101,749 briefly ,mentions that tolerance can be induced by exposing dendritic cells to apoptotic cells in the absence of T helper cells as in the method of Steinman (Immunol Rev 1997, Vol. 156, pp. 25-37). Upon consulting the cited paper it is noted that Steinman contemplates a specialized resident population of dendritic cells within the T-cell areas that express high levels of self-antigen and functional fas ligands capable of inducing CD+4 T cell death (abstract). Steinman speculates that "a lack of CD+4 helper T cells may in turn be pivotal for maintaining the silence of those self-reactive B cells and CD8+ killer cells that escape central deletion in the marrow or the thymus". however, none of the provisional applications provide adequate written description of a method wherein T-cell help is eliminated by methods other than the simple exclusion of T-helper cells from the dendritic cells in the presence of the apoptosis cells.

Accordingly, the instant application will be given the effective filing date of February 19, 1999.

Claims 4 and 15-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 4 has been amended to incorporate the limitations of achieving the absence of effective CD4 T cell help by including prior to or in step c, at least one agent that inhibits or eliminates effective CD 4 T cell help. Applicant has pointed out text by page and line number to support this amendment, however, it is noted that said text describes exposure of a co-culture of dendritic cells and apoptotic cells, and therefore does not provide support for the limitation of "prior to" step c.

Claims 1, 2, 19, 21, 22 are rejected under 103(a) as being unpatentable over Albert et al (Journal of Experimental Medicine, 1998, Vol. 188, pp. 1359-1368, cited in a previous Office action) in view of Albert et al (Nature, 1998, Vol. 392, pp. 86-89) and Heath et al (Journal of Experimental Medicine, 1998, Vol. 187, pp. 1549-1553).

The specific embodiments of the claims are recited in the previous Office action. Albert et al (JEM) teach that dendritic cells phagocytose apoptotic cells and cross present antigens from the apoptotic cells to cytotoxic T-lymphocytes (abstract). Albert et al teach that dendritic cells can acquire antigens from tumors, transplants, infected cells and self tissues for stimulation or tolerization of CTLs (abstract), thus fulfilling the specific limitation of claim 19 specifying the types of antigen for which tolerance might be evoked. Albert et al teach the isolation of dendritic cells from peripheral blood and the use of monocyte conditioned medium (MCM) as a maturation factor for the dendritic cells thus fulfilling the specific embodiments of claim 2 (page 1360, first column, lines 12-14 under the heading of "Preparation of Cells"). Albert et al also teach that on days 10 and 11, the cells were of the mature phenotype CD14-, CD83+ and HLA-DRhi (page 1360, first column, lines 15-17 under the heading "Preparation of Cells"). Albert et

al also teach the maturation factors of LPS, ceramide, CD40L, TNF-alpha and PGE2 in addition to macrophage conditioned medium (page 1359, second column, lines 13-17). Albert et al teach that the co-culture of immature dendritic cells with apoptotic cells in the presence of macrophage conditioned medium , a maturation stimulus for dendritic cells, made apoptotic cells and even better target for cross-presentation of antigen (page 1362, second column, lines 4-8).

Albert et al do not teach the induction of tolerance by the exposure of dendritic cells to apoptotic cells in the absence of effective CD4 T cell help.

Albert et al (Nature) teach the cross-priming of T-cells via apoptotic cells which are phagocytosed by dendritic cells (page 88, second column, lines 27-35). Albert et al teach that tolerance to an antigen may be dependent upon apoptotic cell death followed by antigen presentation by dendritic cells (page 88, second column, lines 35-38, 40-42). Albert et al conclude that the apoptosis dependent pathway has the potential to be manipulated to modulate immune response (page 88, second column, lines 43-46).

Heath et al teach that a number of experimental models have revealed that CD4 T cell help is important for the induction of CTL (page 1551, second column, lines 29-33). Heath et al propose that CD4 T cell help determines if a T cell which has been exposed to a dendritic cell presenting antigen will be "cross tolerized" versus "cross-primed" (page 1551, second column, line 12 and lines 33-35).

It would have been prima facie obvious at the time the invention was made to expose the dendritic cells to apoptotic cells in the absence of effective T-cell help in order to induce tolerance to the antigens made available by the apoptotic cell. One of skill in the art would have been motivated to do so by the teachings of Albert et al (Nature) on the induction of a tolerogenic response by presentation of apoptotic cells by dendritic cells, and the teachings of Heath et al who suggest that lack of CD4 T cell help can result in cross-tolerization to antigens from apoptotic cells taken up by dendritic cells.

Applicant argues that the above combination is not the claimed invention, because the above combination relies of the apoptosis of T cells after activation by the dendritic cells, whereas the instant invention relies on the direct interaction between the dendritic cell and the T cell. This has been considered but not found persuasive. Only claim 4 requires that the agent for

elimination of effective CD4 T cell help be eliminated from the dendritic cell before exposure to the T-cells.

All other rejections and objections as set forth in the previous Office action are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 11 am to 10 pm, except Wed, Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
8/8/2005

KAREN A. CANELLA PH.D
PRIMARY EXAMINER